VOLUME 33 · NUMBER 23 · AUGUST 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study

Owen A. O'Connor, Steven Horwitz, Tamás Masszi, Achiel Van Hoof, Peter Brown, Jeannette Doorduijn, Georg Hess, Wojciech Jurczak, Poul Knoblauch, Shanta Chawla, Gajanan Bhat, Mi Rim Choi, Jan Walewski, Kerry Savage, Francine Foss, Lee F. Allen, and Andrei Shustov

Owen A. O'Connor, Columbia University Medical Center; Steven Horwitz, Memorial Sloan Kettering Cancer Center, New York, NY; Tamás Masszi, St Istvan and St Laszlo Hospital, Budapest, Hungary; Achiel Van Hoof, General Hospital St-Jan, Brugge, Belgium; Peter Brown, Rigshospitalet; Poul Knoblauch, Topotarget, Copenhagen, Denmark; Jeannette Doorduijn, Erasmus Medical Center Cancer Institute, Rotterdam, the Netherlands; Georg Hess, Johannes Gutenberg-University, Mainz, Germany; Wojciech Jurczak, Jagiellonian University, Krakow; Jan Walewski, Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland; Shanta Chawla, Gajanan Bhat, Mi Rim Choi, and Lee F. Allen, Spectrum Pharmaceuticals, Irvine, CA; Kerry Savage, British Columbia Cancer Agency Centre, Vancouver, British Columbia, Canada; Francine Foss, Yale Cancer Center, New Haven, CT; and Andrei Shustov, University of Washington Medical Center, Seattle, WA.

Published online ahead of print at www.jco.org on June 22, 2015.

RC Processed as a Rapid Communication manuscript.

Supported by Spectrum Pharmaceuticals (which also provided medical writing support) and the Columbia University Lymphoma Research Fund.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Owen A. O'Connor, MD, PhD, Columbia University Medical Center, 51 West 51st St, Suite 200, New York, NY 10019; e-mail: oo2130@columbia.edu.

0732-183X/15/3323w-2492w/$20.00

DOI: 10.1200/JCO.2014.59.2782

A B S T R A C T

Purpose
Peripheral T-cell lymphomas (PTCLs) represent a diverse group of non-Hodgkin lymphomas with a poor prognosis and no accepted standard of care for patients with relapsed or refractory disease. This study evaluated the efficacy and tolerability of belinostat, a novel histone deacetylase inhibitor, as a single agent in relapsed or refractory PTCL.

Patients and Methods
Patients with confirmed PTCL who experienced progression after ≥ one prior therapy received belinostat 1,000 mg/m^2 as daily 30-minute infusions on days 1 to 5 every 21 days. Central assessment of response used International Working Group criteria. Primary end point was overall response rate. Secondary end points included duration of response (DoR) and progression-free and overall survival.

Results
A total of 129 patients were enrolled, with a median of two prior systemic therapies. Overall response rate in the 120 evaluable patients was 25.8% (31 of 120), including 13 complete (10.8%) and 18 partial responses (15%). Median DoR by International Working Group criteria was 13.6 months, with the longest ongoing patient at ≥ 36 months. Median progression-free and overall survival were 1.6 and 7.9 months, respectively. Twelve of the enrolled patients underwent stem-cell transplantation after belinostat monotherapy. The most common grade 3 to 4 adverse events were anemia (10.8%), thrombocytopenia (7%), dyspnea (6.2%), and neutropenia (6.2%).

Conclusion
Monotherapy with belinostat produced complete and durable responses with manageable toxicity in patients with relapsed or refractory PTCL across the major subtypes, irrespective of number or type of prior therapies. These results have led to US Food and Drug Administration approval of belinostat for this indication.

J Clin Oncol 33:2492-2499. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) represent a heterogeneous group of aggressive lymphoid malignancies constituting approximately 10% of non-Hodgkin lymphoma cases in the Western population. They are associated with inferior treatment outcomes compared with B-cell lymphomas and have a 5-year-survival < 32%.[1,2] First-line PTCL treatment strategies have largely been adopted from treatment paradigms for aggressive B-cell lymphomas, but they have proven less effective in patients with PTCL. Anthracycline-based regimens, predominantly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), sometimes including etoposide (CHOEP or EPOCH), although commonly used as first-line therapy, typically do not produce durable remissions across PTCL subtypes.[3-7]

T-cell lymphomas (TCLs) have recently emerged as diseases having marked epigenetic dysregulation, which partially explains their sensitivity to histone deacetylase (HDAC) inhibitors. The identification of pathogenetic features affecting DNA methylation (*TET2*, *IDH1/2*, *DNMT3*) or histone remodeling in TCL may portend sensitivity to drugs affecting this biology.[8,9] HDACs play multiple roles in cancer pathogenesis, regulating cellular processes involved in cancer-cell differentiation, proliferation, migration, and survival.[10,11] HDAC inhibitors are pleiotropic drugs simultaneously targeting multiple signaling pathways essential for tumor-cell survival. Early insights into the mechanism of action of HDAC inhibitors have focused on their role in facilitating chromatin condensation and decondensation and thus gene transcription. More recently, they have been thought to mediate post-translational modifications of various histone and nonhistone proteins, likely accounting for their principal mode of action.

Three drugs have received accelerated approval in the United States for the treatment of relapsed or refractory PTCL. Pralatrexate (folate antagonist), romidepsin (HDAC inhibitor), and brentuximab vedotin (antibody–drug conjugate directed to CD30 protein) were approved based on nonrandomized phase II studies, with overall response rates (ORRs) of 29% (all PTCL), 25% (all PTCL), and 86% (systemic anaplastic large-cell lymphoma [ALCL] only), respectively.[12-14] Although these agents represent an advance in relapsed and refractory PTCL treatment, most patients with PTCL continue to experience relapse.[3,12,13] In addition, these drugs have unique toxicity profiles (eg, thrombocytopenia for pralatrexate and romidepsin and peripheral sensory neuropathy for brentuximab), limiting their use in select patients. Thus, durable, well-tolerated disease control is achieved in only a minority of patients, creating a need for additional effective treatment options. The recent emergence of several new drugs specifically active in TCL creates a unique opportunity to combine these agents and potentially generate novel first-line treatment platforms with superior outcomes.

Romidepsin is an HDAC inhibitor that more potently inhibits class I HDACs 1, 2, and 3, with modest inhibitory activity in class II HDACs 4 and 6.[15-17] Belinostat is a hydroxamic acid–derived pan-HDAC inhibitor that broadly inhibits all zinc-dependent HDAC enzymes, with high affinity for class I HDACs 1, 2, and 3, but also class II HDACs 6, 9, and 10 and class IV HDAC 11.[15,18] Although it is not yet entirely clear which HDAC enzymes, when inhibited, account for the activity of these drug in PTCL, one presumption is that the broader the spectrum of inhibition, the better the efficacy. What remains intriguing is that pan-class I and II HDAC inhibitors seem to be reproducibly active even in heavily pretreated patients with PTCL.[19-21]

In an early phase II study, belinostat produced an ORR of 25% in heavily pretreated patients with relapsed or refractory PTCL (n = 24) and 14% in patients with cutaneous TCL (n = 29). Unlike data reported for other HDAC inhibitors, this study also confirmed a highly favorable safety profile for belinostat.[22] The pivotal BELIEF (A Multicenter, Open Label Trial of Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma) study, a phase II study of belinostat in patients with relapsed or refractory PTCL, was therefore initiated.

PATIENTS AND METHODS

Study Design and Treatment

The BELIEF study was a phase II, nonrandomized, open-label study of single-agent belinostat in patients with relapsed or refractory PTCL. Patients received belinostat monotherapy (1,000 mg/m^2) intravenously (IV) over 30 minutes on days 1 to 5 every 21 days. Treatment was administered until death, progressive disease (PD), unacceptable toxicity, hematopoietic stem-cell transplantation (HSCT), loss to follow-up, or patient or investigator decision. Two dose reductions for toxicity were permitted in 25% increments, after which belinostat was discontinued. Interruption of belinostat for > 42 days also resulted in discontinuation.

Primary end point was ORR (complete [CR] plus partial response [PR]) based on central response assessment by the independent review committee.[23] Secondary end points included duration of response (DoR), time to response (TTR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS).

The study protocol was approved by institutional review boards and/or ethics committees at all sites. Study conduct followed International Conference on Harmonisation Guidelines for Good Clinical Practice, including written informed consent and data monitoring.

Patients

Eligible patients were age ≥ 18 years with histologically confirmed PTCL based on local pathology review, which was used for belinostat initiation; PTCL subtype was subsequently confirmed by the central pathology review group (Table 1). Patients had relapsed or refractory disease with ≥ one measurable disease site after ≥ one prior systemic treatment and were > 100 days from HSCT. Excluded PTCL subtypes included precursor and adult TCL or leukemia, prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, primary cutaneous ALCL, mycosis fungoides, and Sézary syndrome. Performance status of 0 to 2, life expectancy > 3 months, and adequate hematologic, hepatic, and renal function, including absolute neutrophil count ≥ 1,000/μL and platelets ≥ 50,000/μL, were also required. Patients who had received prior HDAC inhibitor treatment at any time or anticancer therapy within 2 weeks were excluded, as were patients with baseline QT prolongation (> 450 milliseconds) or long QT syndrome.

Study Assessments

Tumor assessments were conducted by the independent review committee per the International Harmonisation Project revision of the International Working Group (IWG) criteria.[23] Assessments were performed at baseline and every 6 weeks for the first 12 months and then every 12 weeks until 2 years from the start of study treatment. Patients with positive baseline bone marrow biopsies had repeat bone marrow biopsies if radiologically assessed with a CR. Radiologic assessments were discontinued on PD or initiation of subsequent anticancer therapy.

Safety assessments included physical examinations, ECGs, adverse event (AE) monitoring, and laboratory parameter changes. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). An independent data monitoring committee monitored safety and met twice during the study, recommending study continuation as planned. ECGs were analyzed independently by eResearch Technologies (Philadelphia, PA).

After discontinuing therapy, patients completed an end-of-treatment visit 30 days after their last belinostat dose. Survival data were collected every 3 months up to 2 years from start of study treatment or until study closure.

Statistical Analysis

Primary study end point of ORR was based on independent review, where a 20% ORR was considered clinically meaningful. Sample size was based on a two-stage optimal design,[24] with a hypothesized ORR of the alternate hypothesis (p1 = 20%) for belinostat and a minimal or uninteresting ORR of null hypothesis (p0 = 9%). If there were < five objective responses in the first 41 evaluable patients, the trial was to be discontinued for futility. Otherwise, the trial was to continue until there were ≥ 100 evaluable patients for primary analysis. This meant that ≥ 59 additional patients would be needed in the second stage.

Including the assumed attrition rate of 20% resulting from nonevaluability, 120 patients were to be enrolled. At least 14 objective responses in 100 evaluable patients were required to confirm the 20% target response rate with a type I error rate of 5% assuming a power of 90% (type II error rate, 10%). Formal interim analysis was conducted by the independent data monitoring committee after 41 evaluable patients received ≥ one belinostat dose. CIs for ORR were calculated using the Clopper-Pearson method (exact interval based on cumulative probabilities of binomial distribution). Time-to-event end points were calculated using the Kaplan-Meier method.

Table 1. Baseline Demographic and Clinical Characteristics of Evaluable Population (N = 120)

Characteristic	No. (%)
Sex	
Male	62 (51.7)
Female	58 (48.3)
Race	
White	105 (87.5)
Black	7 (5.8)
Asian	3 (2.5)
Latin	3 (2.5)
Other	2 (1.7)
Age, years	
< 65	61 (50.8)
≥ 65	59 (49.2)
Median	64.0
Range	29 to 81
ECOG	
0 to 1	93 (77.5)
2	26 (21.7)
3*	1 (0.8)
PTCL subtype by central review	
PTCL-NOS	77 (64.2)
AITL	22 (18.3)
ALCL	
ALK negative	13 (10.8)
ALK positive	2 (1.7)
Enteropathy-associated TCL	2 (1.7)
Extranodal NK TCL, nasal type	2 (1.7)
Hepatosplenic TCL	2 (1.7)
Bone marrow involvement	
No	65 (54.2)
Yes	35 (29.2)
Indeterminate/not assessed	20 (16.7)
Time from initial diagnosis, months	
Median	12.0
Range	2.6 to 266.4
Ann Arbor stage at study entry	
IA	5 (4.2)
IIA	7 (5.8)
IIB	4 (3.3)
IIIA	23 (19.2)
IIIB	19 (15.8)
IVA	35 (29.2)
IVB	25 (20.8)
Unknown	2 (1.7)
No. of prior systemic therapies	
Median	2.0
Range	1 to 8
All prior systemic therapies	
Multiagent regimen	
CHOP or CHOP-like	116 (96.7)
Platinum containing	38 (31.7)
Other	44 (36.7)
Single-agent regimen	
Pralatrexate	10 (8.3)
Corticosteroids	4 (3.3)
Other	20 (16.7)
Stem-cell transplantation	25
Autologous	23
Allogeneic	2
Most recent prior systemic therapy	
Multiagent regimen	
CHOP or CHOP-like	53 (44.2)
Platinum containing	16 (13.3)
Other	33 (27.5)
Single-agent regimen	
Pralatrexate	6 (5.0)
Corticosteroids	1 (0.8)
Other	11 (9.2)
Baseline platelet count (all ≥ 50,000/μL)	
< 100,000	20 (16.7)
≥ 100,000	100 (83.3)

(continued in next column)

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; NK, natural killer; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; TCL, T-cell lymphoma.
*Patient had ECOG 1 at screening but ECOG 3 on day 1 of cycle one.

DoR was calculated using two methods, beginning when response criteria were first met (CR or PR). End date for the first method (per IWG criteria) was the first subsequent date that relapse or progression was documented, with patients who died censored at their last tumor assessment (ie, death was not event).[23] End date for the second method was date of either PD or death.

TTP was time from first belinostat administration to PD per independent review committee. PFS was time from first belinostat administration to PD per independent review committee or death resulting from any cause. Patients without PD or death or who initiated subsequent anticancer therapy before PD or death were censored at their last tumor assessment. Patients without postbaseline tumor assessments were censored on first treatment day. OS was time from first belinostat administration to date of death. Patients who were alive at the analysis point were censored at last date they were known to be alive. All results presented reflect data analysis cutoff of August 2012.

RESULTS

Patient Characteristics

Between May 2009 and August 2011, 129 patients with relapsed or refractory PTCL were enrolled and treated at 62 investigational sites across the United States, Europe, Canada, Israel, and South Africa. The central pathology review group histologically confirmed PTCL in 120 patients (evaluable population); the majority (64.2%) had PTCL not otherwise specified. The study enrolled patients with low baseline platelet counts or more aggressive PTCL subtypes; no patients with mycosis fungoides were enrolled.

A majority (87.5%) of patients were white, 51% were men, and median age was 64.0 years (range, 29 to 81 years; Table 1). Evaluable patients had received a median of 2.0 prior systemic therapies (range, one to eight) comprising mostly multiagent regimens, with 18.3% of patients having received ≥ three. For most patients (96.7%), previous CHOP or CHOP-like multiagent therapies had failed; 20.8% of evaluable patients had undergone prior HSCT.

Efficacy

Primary efficacy analysis was based on independent review committee–assessed response. Belinostat demonstrated an ORR of

Table 2. Summary of Efficacy in Evaluable Population (N = 120)

Response	Response by IRC No. (%)	Response by Local Investigator No. (%)
ORR (CR + PR)	31 (25.8)	27 (22.5)
Best response		
CR	13 (10.8)	11 (9.2)
PR	18 (15.0)	16 (13.3)
SD	18 (15.0)	29 (24.2)
PD	47 (39.2)	53 (44.2)
NE	24 (20.0)*	11 (9.2)
Median TTR, weeks	5.6	6.3
Range	4.3 to 50.4	4.1 to 44.1
Median DoR by IWG, months	13.6†	12.1
95% CI	4.5 to 29.4	4.7 to 19.8
Median TTP, months	2.0	2.0
95% CI	1.5 to 2.8	1.5 to 2.9
Median PFS, months	1.6	1.8
95% CI	1.4 to 2.7	1.5 to 2.7
Median OS, months	7.9	
95% CI	6.1 to 13.9	

Pretreatment Characteristic	ORR by IRC No. (%)	95% CI
PTCL subtype by central review		
PTCL-NOS	18 of 77 (23.3)	14.5 to 34.4
AITL	10 of 22 (45.5)	24.4 to 67.8
ALCL		
ALK negative	2 of 13 (15.3)	1.9 to 45.4
ALK positive	0 of 2 (0.0)	0.0 to 84.2
Enteropathy-associated TCL	0 of 2 (0.0)	0.0 to 84.2
Extranodal NK TCL, nasal	1 of 2 (50.0)	1.3 to 98.7
Hepatosplenic TCL	0 of 2 (0.0)	0.0 to 84.2
Baseline bone marrow involvement		
Yes	20 of 65 (30.8)	19.9 to 43.4
No	8 of 35 (22.9)	10.4 to 40.1
Indeterminate	2 of 8 (25.0)	3.2 to 65.1
Not assessed	1 of 12 (8.3)	0.2 to 38.5
Baseline platelet count (all ≥ 50,000/μL)		
≥ 100,000	28 of 100 (28.0)	19.5 to 37.9
< 100,000	3 of 20 (15.0)	3.2 to 37.9
Response to last systemic therapy		
CR	14 of 29 (48.2)	29.4 to 67.5
PR	6 of 21 (28.6)	11.3 to 52.2
SD	5 of 20 (25.0)	8.7 to 49.1
PD	3 of 37 (8.1)	1.7 to 21.9
NE	3 of 11 (27.2)	6.0 to 61.0
Unknown	0 of 2 (0.0)	0.0 to 84.2
ECOG performance status		
0	12 of 41 (29.3)	16.1 to 45.5
1	8 of 52 (15.4)	6.9 to 28.1
2	11 of 26 (42.3)	23.4 to 63.1
3	0 of 1 (0.0)	0.0 to 97.5

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; CR, complete response; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; IWG, International Working Group; NE, not evaluable; NK, natural killer; NOS, not otherwise specified; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease; TCL, T-cell lymphoma; TTP, time to progression; TTR, time to response.

*Reasons for nonevaluability include occurrence of following before first tumor assessment: PD or death (n = 16), withdrawal or loss to follow-up (n = 6), or study discontinuation (n = 1), as well as one patient who did not have index lesion identified.

†DoR calculated based on first date of response to PD or death was 8.4 months (95% CI, 4.5 to 29.4).

25.8% (n = 31; CR, 13; PR, 18); ORR assessed by local investigators was 22.5% (Table 2). Sixty-one percent of responding patients demonstrated an objective response within 30 to 45 days of initial dosing, with a median TTR of 5.6 weeks (range, 4.3 to 50.4 weeks). Seven patients experienced PRs that subsequently converted to CRs within 1 to 18 months with further belinostat treatment. Responses were durable, with ongoing therapy leading to a median DoR of 13.6 months

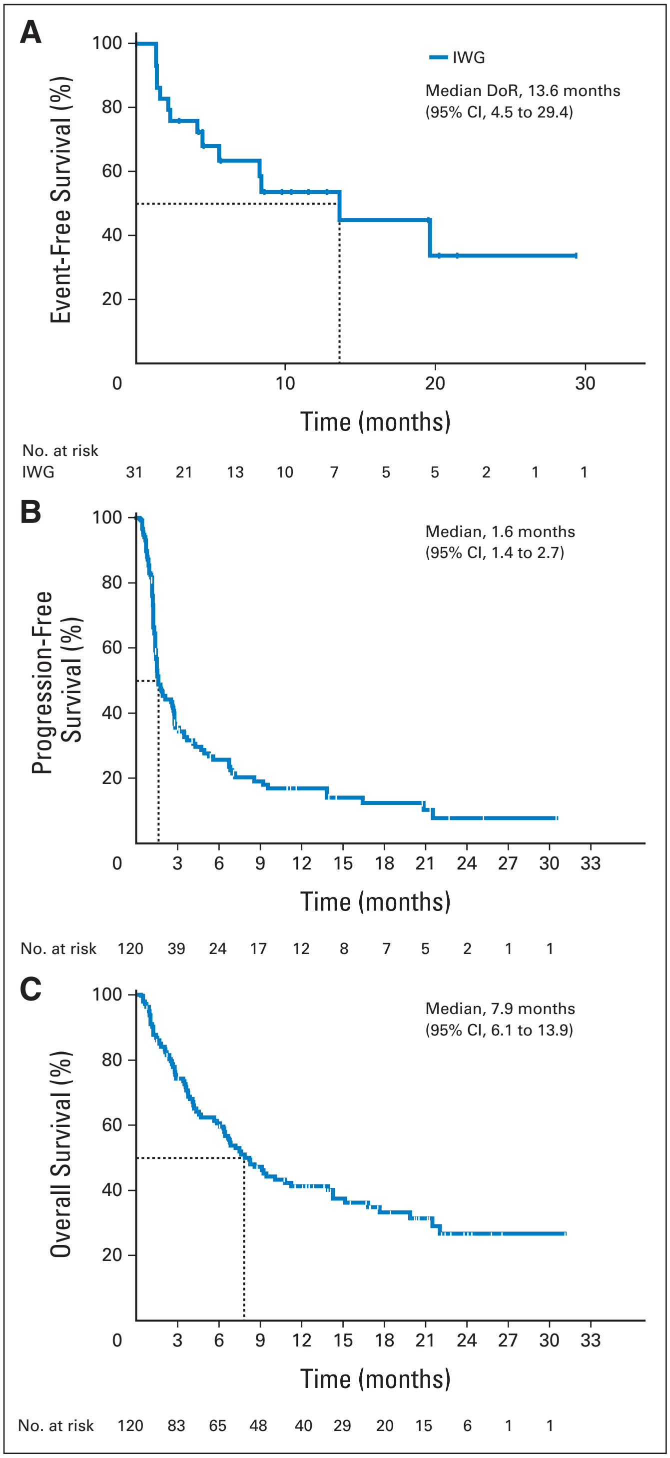

Fig 1. Kaplan-Meier estimates. (A) Duration of response (DoR), (B) progression-free survival, and (C) overall survival by International Working Group (IWG) criteria per independent review committee assessment.

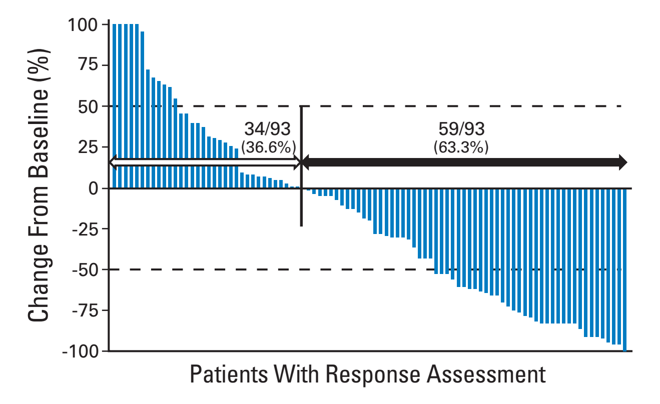

Fig 2. Maximum change from baseline sum of products of greatest diameters.

(95% CI, 4.5 to 29.4) per IWG criteria (Fig 1A). In the subgroup of patients achieving CRs (n = 13), median DoR was not reached but exceeded 29 months. The longest response was ongoing at 36+ months in a patient with angioimmunoblastic T-cell lymphoma (AITL); median DoR based on date of first response to PD or death was 8.4 months (95% CI, 4.5 to 29.4). Among responding patients treated with belinostat, probability of maintaining response was 57.7% at 6 months, 48.8% at 1 year, and 32.6% at 2 years.

Clinically meaningful responses were observed in many PTCL subtypes, including AITL (n = 22; ORR, 45.5%), and in patients with baseline bone marrow involvement (n = 35; ORR, 30.8%), and in those with nonresponse to last prior systemic therapy (n = 33; ORR, 15.7%; Table 2).[12,13,25] Decreased tumor volume was observed in 63.3% of patients with post-treatment assessments based on the difference in the sum of the products of greatest diameters between baseline and post-treatment assessments (n = 93; Fig 2).

Probability of surviving and being progression free at 1 year was 19.3%. Median PFS was 1.6 months (95% CI, 1.4 to 2.7; Fig 1B), median TTP was 2.0 months (95% CI, 1.5 to 2.8), and median OS was 7.9 months (95% CI, 6.1 to 13.9; Fig 1C). Nearly 40% (n = 46) of patients were censored for OS, because they were alive at data cutoff, and seven patients continued to receive belinostat treatment (CR, 5; PR, 1; stable disease, 1). Importantly, belinostat treatment enabled 12 patients to subsequently undergo HSCT, 10 of whom remained alive at data cutoff (OS range, 9.4 to 22.9 months).

Safety

Belinostat treatment was well tolerated, with most patients (113 of 129; 87.6%) remaining at the target dose (1,000 mg/m^2). Relative dose-intensity (doses administered *v* planned) was 98.3%, and median treatment duration was 7.0 weeks (range, 3.0 to 135.0 weeks), with treatment administered for ≥ 6 months in 17.8% of patients and ≥ 1 year in 10.1%.

Treatment-emergent AEs (TEAEs) occurred in 96.9% of patients and were generally mild to moderate in severity. The most common TEAEs were nausea (41.9%), fatigue (37.2%), and pyrexia (34.9%; Table 3); 12.4% of patients experienced TEAEs resulting in dose reduction. Overall, 16.3% of patients had thrombocytopenia, but importantly, grade 3 to 4 thrombocytopenia occurred in only 7.0%. Two patients had a dose reduction because of prolonged QTc or increased transaminases; no other single AE resulted in dose modification for ≥ one patient.

Table 3. Treatment-Emergent SAEs in Safety Population (n = 129)

	NCI CTCAE Grade		
MedDRA Preferred Term	All Grades No. (%)	1 to 2 No. (%)	3 to 4 No. (%)
SAEs (> two patients)	61 (47.3)	20 (15.5)	45 (34.9)
Pneumonia	9 (7.0)	1 (0.8)	7 (5.4)
Pyrexia	7 (5.4)	7 (5.4)	0 (0)
Infection	4 (3.1)	0 (0)	4 (3.1)
Anemia	3 (2.3)	0 (0)	3 (2.3)
Increased blood creatinine	3 (2.3)	3 (2.3)	0 (0)
Multiorgan failure	3 (2.3)	0 (0)	0 (0)
Thrombocytopenia	3 (2.3)	0 (0)	3 (2.3)
Related SAEs (> one patient)	27 (20.9)	11 (8.5)	18 (14.0)
Increased blood creatinine	3 (2.3)	3 (2.3)	0 (0)
Pyrexia	3 (2.3)	3 (2.3)	0 (0)
Thrombocytopenia	3 (2.3)	0 (0)	3 (2.3)
Anemia	2 (1.6)	0 (0)	2 (1.6)
Infection	2 (1.6)	0 (0)	2 (1.6)
Pneumonia	2 (1.6)	0 (0)	2 (1.6)

AEs Associated With Death Within 30 Days of Last Dose	Patients No. (%)	Treatment Related No. (%)
Total deaths	22 (17.1)	1 (0.8)
Disease progression	12 (9.3)	0
AEs	10 (7.8)	1 (0.8)
Multiorgan failure	3 (2.3)	0
Cardiac failure	2 (1.6)	0
Lung infection	1 (0.8)	0
GI hemorrhage	1 (0.8)	0
Euthanasia	1 (0.8)	0
Hepatic failure	1 (0.8)	1 (0.8)
Shock	1 (0.8)	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; SAE, serious adverse event.
*Independent central review of ECGs confirmed only two patients with grade 3 prolonged ECG QT.

Related TEAEs were reported in 83.7% of patients and included nausea (38.0%), fatigue (28.7%), and vomiting (24.0%). Grade 3 to 4 TEAEs were reported in 61.2%; those occurring in ≥ 5% of patients were mostly hematologic, including anemia (10.9%), thrombocytopenia (7.0%), dyspnea and neutropenia (6.2% each), and fatigue and pneumonia (5.4% each). Treatment withdrawal for TEAEs occurred in 19.4% of patients and was considered treatment related in 10.9%. TEAEs leading to withdrawal for ≥ one patient included multiple organ failure, fatigue, anemia, and febrile neutropenia (n = 2 [1.6%] each).

Serious AEs (SAEs) occurred in 47.3% of patients, with nonhematologic SAEs occurring more frequently than hematologic (Table 3). SAEs reported for ≥ one patient included increased creatinine, pyrexia, and thrombocytopenia (n = 2 [1.6%] each).

Twenty-two patients (17.1%) died (Table 3). Twelve deaths (9.3%) were attributed to PD and the remaining 10 (7.8%) to TEAEs within 30 days of last belinostat dose. All deaths were considered unrelated to belinostat, except for one patient who had a complex medical history, tolerated nine cycles of belinostat without complications, and had elevated liver function tests at the start of cycle 10 that subsequently led to death as a result of toxic liver failure.

Independent central review of ECG data identified two patients with grade 3 QT prolongation and concluded that belinostat had no effect on cardiac repolarization. Pharmacokinetic and pharmacodynamic analyses showed no correlation between belinostat concentration and QTc changes from baseline; no clinically relevant changes in other ECG parameters were noted.

DISCUSSION

Unfortunately, current treatment options for patients with relapsed or refractory PTCL induce responses in < 30% of patients, and long-term survival is relatively poor. In addition, approximately two thirds of the overall relapsed or refractory PTCL population are not candidates for HSCT.[26,27] A study in relapsed and refractory PTCL (n = 153) reported median OS and PFS of 5.5 and 3.1 months, respectively.[26] Better outcomes were achieved by patients who experienced relapse after attaining a CR from systemic therapy (47%), with median OS and PFS of 10.6 and 6.4 months, respectively. Patients who did not respond to prior chemotherapy (29%) had a median OS of only 1.3 months, highlighting the urgent need for new drugs in this patient population.

The recent approval of two drugs for patients with relapsed or refractory PTCL, with response rates of 29% (pralatrexate) and 25% (romidepsin), has created new opportunities for disease control. Furthermore, these agents have distinct toxicity profiles that include cytopenias, increased risk of infection, and mucositis, which may limit dosing and potential inclusion in combination treatment regimens. A third approved agent, brentuximab vedotin, demonstrated an ORR of 86% in systemic ALCL and 54% in AITL, but it has been approved only for systemic ALCL and is associated with peripheral sensory neuropathy and cases of progressive multifocal leukoencephalopathy.[28] The BELIEF study has established that belinostat produces a meaningful ORR of approximately 26%, with CR rate of 11%, and has a favorable toxicity profile, producing substantially less myelosuppression and no mucositis compared with AEs reported with other approved agents (Table 4).

Multiple data have established that TCLs are diseases enriched for epigenetic mutations leading to dysregulation of gene expression. Inactivating mutations in the *TET2* gene have been reported

Table 4. Phase II Study Results From United States Supporting Prescribing Information for Agents Approved for Relapsed or Refractory PTCL

Result	Belinostat	Pralatrexate	Romidepsin	Brentuximab Vedotin*
No. of patients (response evaluable of those enrolled)	120 of 129	109 of 111	130 of 131	58 of 58*
Central review of response	Yes	Yes	Yes	Yes
ORR	26% (CR + PR)	27% (CR + CRu + PR)	26% (CR + CRu + PR)	86% (CR + PR)*
Nonhematologic AEs†	Nausea (42%) Fatigue (37%) Pyrexia (35%) Vomiting (29%) Constipation (23%) Diarrhea (23%) Dyspnea (22%) Rash (20%) Peripheral edema (20%)	Mucositis (70%) Nausea (40%) Fatigue (36%) Constipation (33%) Pyrexia (32%) Edema (30%) Cough (28%) Epistaxis (26%) Vomiting (25%) Diarrhea (21%)	Nausea (59%) Asthenia/fatigue (55%) Vomiting (39%) Diarrhea (36%) Pyrexia (35%) Constipation (30%) Anorexia (28%) Dysgeusia (21%)	Peripheral sensory neuropathy (53%) Fatigue (41%) Nausea (38%) Pyrexia (38%) Rash (31%) Pain (28%) Diarrhea (29%)
Hematologic AEs‡	Anemia (32%) Thrombocytopenia (16%)	Thrombocytopenia (41%) Anemia (34%) Neutropenia (24%) Leukopenia (11%)	Thrombocytopenia (41%) Neutropenia (30%) Anemia (25%) Leukopenia (12%)	Neutropenia (55%) Anemia (52%) Thrombocytopenia (16%)
Warning or precaution				
Myelosuppression	X	X	X	X
Infection	X		X	X
Hepatotoxicity	X	X		
Tumor lysis syndrome	X		X	X
GI toxicity	X			
Mucositis		X		
Folic acid or vitamin B_{12} required		X		
Renal toxicity		X		
ECG changes			X	
Peripheral neuropathy				X
Infusion reactions				X
Stevens-Johnson syndrome				X
PML				X (boxed warning)§

Abbreviations: AE, adverse event; CR, complete response; CRu, complete response unconfirmed; ORR, overall response rate; PML, progressive multifocal leukoencephalopathy; PR, partial response; PTCL, peripheral T-cell lymphoma.
*Patients with anaplastic large-cell lymphoma only.
†All grades; occurring in ≥ 20% of patients.
‡Occurring in ≥ 10% of patients.
§Complete boxed warning states John Cunningham virus infection resulting in PML and death can occur in patients.

in approximately half of AITL patient cases and one third of PTCL patient cases, but they are essentially absent in other PTCL subtypes.[29] Similarly, mutations in *IDH2* were found in 20% to 45% of patient cases of AITL, whereas *DNMT3* mutations were only variably noted in patients with AITL and PTCL not otherwise specified. Collectively, these data point to fundamental epigenetic defects in TCL.

Approval of HDAC inhibitors only in TCL, coupled with enrichment of molecular and genetic defects regulating histone and DNA methylation, suggests that HDAC inhibitor–based platforms could form the basis of new treatment paradigms for PTCL. Although the precise mechanism of action of HDAC inhibitors is not defined, as a class, HDAC inhibitors have clear reproducible activity in this disease setting.[8,9,30-32]

Understanding why HDAC inhibitors have such reproducible activity in PTCL has been the subject of intense research. Several HDACs, particularly HDAC 2 and 6, are more highly expressed in aggressive forms of cutaneous TCL and may be associated with inferior outcome.[33] Identification of these and other dysregulated epigenetic features in patients with PTCL may become useful biomarkers in the future to identify patients most likely to benefit from this class of drugs. A recent preclinical study demonstrated the synergistic effect of simultaneously inhibiting defined combinations of HDAC isoforms on TCL-cell growth in vitro.[34]

The strategy of combining HDAC inhibitors with antitumor agents represents a promising opportunity to develop new treatment regimens for patients with PTCL.[35] However, it has been difficult to incorporate novel agents into conventional chemotherapy regimens (eg, CHOP, gemcitabine-based regimens), which are already associated with high rates of pancytopenia. Such combinations have often resulted in dose- and/or treatment-limiting myelosuppression.[36,37] For example, results from a phase Ib/II study of CHOP plus romidepsin versus CHOP (N = 18) demonstrated a high incidence of hematologic toxicity in the romidepsin arm.[38,39]

Data from the BELIEF study demonstrate that belinostat is an active agent in PTCL. In addition to responses in approximately 26% of patients, nearly two thirds of patients experienced disease reduction (Fig 2). Remissions were durable, with a median DoR of 13.6 months by IWG criteria. Belinostat was tolerated (median dose-intensity, 98.5%) by patients who would not have been candidates for treatment with the other approved treatments (eg, those with low baseline platelet counts [$< 100{,}000/\mu L$]), with an ORR of 15.0% in this challenging patient population.

Belinostat monotherapy was well tolerated in this heavily pretreated population, with few patients requiring dose reductions (12.4%). Low incidence of grade 3 to 4 hematologic toxicities with belinostat (thrombocytopenia, 7%; neutropenia, 6.2%; anemia, 10.9%) suggests that it could be combined safely with cytotoxic chemotherapies. Given its highly favorable AE profile, it may be possible to incorporate belinostat into conventional or novel regimens with limited toxicity, potentially leading to improved efficacy.

In summary, the BELIEF study has demonstrated belinostat to be active in PTCL. Its safety profile suggests that it could be combined favorably with other regimens or agents (eg, CHOP, pralatrexate, proteasome inhibitors, or antibody–drug conjugates). Approval of active, well-tolerated drugs like belinostat will enable the development of novel treatments that may improve outcome for patients with PTCL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Provision of study materials or patients: Owen A. O'Connor, Achiel Van Hoof, Georg Hess, Wojciech Jurczak, Francine Foss, Andrei Shustov
Collection and assembly of data: Owen A. O'Connor, Steve Horwitz, Tamás Masszi, Achiel Van Hoof, Peter Brown, Jeannette Doorduijn, Georg Hess, Wojciech Jurczak, Poul Knoblauch, Shanta Chawla, Gajanan Bhat, Jan Walewski, Kerry Savage, Francine Foss, Lee F. Allen, Andrei Shustov
Data analysis and interpretation: Owen A. O'Connor, Steve Horwitz, Tamás Masszi, Peter Brown, Wojciech Jurczak, Poul Knoblauch, Gajanan Bhat, Mi Rim Choi, Jan Walewski, Kerry Savage, Francine Foss, Lee F. Allen, Andrei Shustov
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 89:3909-3918, 1997

2. Savage KJ: Peripheral T-cell lymphomas. Blood Rev 21:201-216, 2007

3. O'Leary HM, Savage KJ: Novel therapies in peripheral T-cell lymphomas. Curr Oncol Rep 10: 404-411, 2008

4. Armitage JO: The aggressive peripheral T-cell lymphomas: 2013. Am J Hematol 88:910-918, 2013

5. Chen AI, Advani RH: Beyond the guidelines in the treatment of peripheral T-cell lymphoma: New drug development. J Natl Compr Canc Netw 6:428-435, 2008

6. Vose J, Armitage J, Weisenburger D: International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. J Clin Oncol 26:4124-4130, 2008

7. Moskowitz A, Lunning M, Horwitz S: How I treat the peripheral T-cell lymphomas. Blood 123: 2636-2644, 2014

8. Horwitz SM: The emerging role of histone deacetylase inhibitors in treating T-cell lymphomas. Curr Hematol Malig Rep 6:67-72, 2011

9. Atadja P: Development of the pan-DAC inhibitor panobinostat (LBH589): Success and challenges. Cancer Lett 280:233-241, 2009

10. Kristeleit R, Fong P, Aherne GW, et al: Histone deacetylase inhibitors: Emerging anticancer therapeutic agents? Clin Lung Cancer 7:S19-S30, 2005

11. Minucci S, Pelicci PG: Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev Cancer 6:38-51, 2006

12. O'Connor OA, Pro B, Pinter-Brown L, et al: Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J Clin Oncol 29:1182-1189, 2011

13. Coiffier B, Pro B, Prince HM, et al: Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 30:631-636, 2012

14. Pro B, Advani R, Brice P, et al: Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: Results of a phase II study. J Clin Oncol 30:2190-2196, 2012

15. Furumai R, Matsuyama A, Kobashi N, et al: FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases. Cancer Res 62: 4916-4921, 2002

16. Gryder BE, Sodji QH, Oyelere AK: Targeted cancer therapy: Giving histone deacetylase inhibitors all they need to succeed. Future Med Chem 4:505-524, 2012

17. Lane AA, Chabner BA: Histone deacetylase inhibitors in cancer therapy. J Clin Oncol 27:5459-5468, 2009

18. Miller TA, Witter DJ, Belvedere S: Histone deacetylase inhibitors. J Med Chem 46:5097-5116, 2003

19. Gimsing P, Hansen M, Knudsen LM, et al: A phase I clinical trial of the histone deacetylase inhibitor belinostat in patients with advanced hematological neoplasia. Eur J Haematol 81:170-176, 2008

20. Plumb J, Finn P, Williams R, et al: Pharmacodynamic response and inhibition of growth of human tumor xenografts by the novel histone deacetylase inhibitor PXD101. Mol Cancer Ther 2:721-728, 2003

21. Qian X, LaRochelle W, Ara G, et al: Activity of PXD101, a histone deacetylase inhibitor, in preclinical ovarian studies. Mol Cancer Ther 8:2086-2095, 2006

22. Foss F, Advani R, Duvic N, et al: A Phase II trial of belinostat (PXD101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. Br J Haematol 168:811-819, 2015

23. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007

24. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1-10, 1989

25. Mounier N, Gisselbrecht C, Brière J, et al: Prognostic factors in patients with aggressive non-Hodgkin's lymphoma treated by front-line autotransplantation after complete remission: A cohort study by the Groupe d'Etude des Lymphomas de l'Adulte. J Clin Oncol 22:2826-2834, 2004

26. Mak V, Hamm J, Chhanabhai M, et al: Survival of patients with peripheral T-cell lymphoma after first relapse or progression: Spectrum of disease and rare long-term survivors. J Clin Oncol 31:1970-1976, 2013

27. Lunning MA, Moskowitz AJ, Horwitz S: Strategies for relapsed peripheral T-cell lymphoma: The tail that wags the curve. J Clin Oncol 31:1922-1927, 2013

28. Horwitz SM, Advani RH, Bartlett NL, et al: Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood 123: 3095-3100, 2014

29. Lemonnier F, Couronné L, Parrens M, et al: Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood 120:1466-1469, 2012

30. Whittaker SJ, Demierre MF, Kim EJ, et al: Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 28:4485-4491, 2010

31. O'Connor O, Heaney M, Schwartz L, et al: Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. J Clin Oncol 24:166-173, 2006

32. Jain S, Zain J, O'Connor O: Novel therapeutic agents for cutaneous T-cell lymphoma. J Hematol Oncol 5:24, 2012

33. Zain J, O'Connor O. Targeting histone deacetylases in the treatment of B- and T-cell malignancies. Invest New Drugs 28:S58-S78, 2010 (suppl 1)

34. Deng C, Rodriguez R, McIntosh C, et al: Combination of selective HDAC inhibitors that target specific HDAC isoforms synergistically inhibits T cell lymphoma. Blood 122, 2013 (abstr 5142)

35. Lemoine M, Younes A: Histone deacetylase inhibitors in the treatment of lymphoma. Discov Med 10:462-470, 2010

36. Kansara R, Savage KJ: The problem with cyclophosphamide, doxorubicin, vincristine and prednisone for the treatment of peripheral T-cell lymphoma. Leuk Lymphoma 55:727-729, 2014

37. Evens AM, Rosen ST, Helenowski I, et al: A phase I/II trial of bortezomib combined concurrently with gemcitabine for relapsed or refractory DLBCL and peripheral T-cell lymphomas. Br J Haematol 163:55-61, 2013

38. Delarue R, Zinzani PL, Hertzberg MS, et al: ROCHOP study: A phase III randomized study of CHOP compared to romidepsin-CHOP in untreated peripheral T-cell lymphoma. J Clin Oncol 31:546s, 2013 (suppl 15s; abstr TPS8616)

39. Dupuis J, Morschhauser F, Ghesquieres H, et al: A phase IB/II trial of romidepsin in association with CHOP in patients with peripheral T-cell lymphoma (PTCL): The RO-CHOP study. Hematol Oncol 31, 2013 (suppl; abstr 118)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Owen A. O'Connor
Honoraria: Mundipharma, Takeda Pharmaceuticals, Seattle Genetics, Novartis
Consulting or Advisory Role: Mundipharma, Seattle Genetics, Novartis, Takeda Pharmaceuticals, Spectrum Pharmaceuticals, Allos Therapeutics
Research Funding: Takeda Pharmaceuticals, Seattle Genetics, Acetylon Pharmaceuticals, Celgene, Roche, Spectrum Pharmaceuticals
Travel, Accommodations, Expenses: Takeda Pharmaceuticals, Mundipharma, Acetylon, Seattle Genetics, Spectrum Pharmaceuticals

Steve Horwitz
Consulting or Advisory Role: Celgene, Amgen, Bristol-Myers Squibb, Janssen Pharmaceuticals, Millennium Pharmaceuticals, Spectrum Pharmaceuticals, Seattle Genetics, ADC Therapeutics, Immunogen, Kyowa Hakko Kirin
Research Funding: Celgene, Millennium Pharmaceuticals, Infinity, Kyowa-Kirin, Seattle Genetics, Spectrum Pharmaceuticals
Travel, Accommodations, Expenses: Infinity Pharmaceuticals, RAND

Tamás Masszi
No relationship to disclose

Achiel Van Hoof
No relationship to disclose

Peter Brown
Consulting or Advisory Role: Gilead, Janssen-Cilag
Travel, Accommodations, Expenses: Roche

Jeannette Doorduijn
Consulting or Advisory Role: Celgene, Roche, Janssen
Travel, Accommodations, Expenses: Janssen, Roche, Novartis

Georg Hess
Honoraria: Celgene, CTI, Janssen, Pfizer, Roche
Consulting or Advisory Role: Celgene, CTI, Janssen, Pfizer, Roche
Research Funding: Pfizer (Inst), Mundipharma (Inst)
Travel, Accommodations, Expenses: Janssen, Pfizer, Roche

Wojciech Jurczak
Consulting or Advisory Role: Mundipharma, Sandoz-Novartis, Spectrum Pharmaceuticals, Takeda Pharmaceuticals, Teva
Research Funding: Celgene, Eisai, Gilead, Janssen, Pfizer, Roche, Spectrum Pharmaceuticals, Takeda Pharmaceuticals, Sandoz-Novartis

Poul Knoblauch
Employment: Onxeo
Stock or Other Ownership: Onxeo

Shanta Chawla
No relationship to disclose

Gajanan Bhat
Employment: Spectrum Pharmaceuticals
Stock or Other Ownership: Spectrum Pharmaceuticals

Mi Rim Choi
Employment: Spectrum Pharmaceuticals
Stock or Other Ownership: Spectrum Pharmaceuticals, Amgen

Jan Walewski
Honoraria: Roche, Takeda Pharmaceuticals, Mundipharma, Celgene
Consulting or Advisory Role: Roche, Takeda Pharmaceuticals, Janssen-Cilag, Teva, Boehringer Ingelheim, Celgene, Mundipharma
Research Funding: Roche (Inst), Mundipharma (Inst), Celgene (Inst), GlaxoSmithKline (Inst), Roche/Genentech (Inst), GlaxoSmithKline (Inst), Seattle Genetics (Inst), Gilead Sciences (Inst), Bayer (Inst), Bayer/Onyx Pharmaceuticals (Inst), Boehringer Ingelheim (Inst), Pfizer (Inst), Celltrion (Inst)
Travel, Accommodations, Expenses: Roche, Celgene, Takeda Pharmaceuticals

Kerry Savage
Honoraria: Seattle Genetics, Celgene, Bristol-Myers Squibb
Consulting or Advisory Role: Seattle Genetics, Bristol-Myers Squibb
Research Funding: Roche (Inst)

Francine Foss
Honoraria: Celgene, Seattle Genetics, Spectrum Pharmaceuticals
Speakers' Bureau: Celgene, Seattle Genetics
Research Funding: Celgene (Inst), Infinity (Inst), Millennium Pharmaceuticals (Inst)

Lee F. Allen
Employment: Spectrum Pharmaceuticals
Leadership: Spectrum Pharmaceuticals
Stock or Other Ownership: Spectrum Pharmaceuticals, Pfizer
Consulting or Advisory Role: AMAG Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Duke University Medical Center
Travel, Accommodations, Expenses: AMAG Pharmaceuticals, Spectrum Pharmaceuticals

Andrei Shustov
Honoraria: Celgene
Consulting or Advisory Role: Celgene, Spectrum Pharmaceuticals
Research Funding: Celgene (Inst), Seattle Genetics (Inst), Spectrum Pharmaceuticals (Inst), Millennium Pharmaceuticals (Inst), Pharmacyclics (Inst)

Acknowledgment

We thank Lindsey Lozano, Spectrum Pharmaceuticals, for medical writing assistance.

Presented in part at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013; 13th International Conference on Malignant Lymphoma, Lugano, Switzerland, June 17-20, 2013; and Fifth Annual T-Cell Lymphoma Forum, San Francisco, CA, January 24-26, 2013.